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DEVELOPMENTS IN INTERNAL MEDICINE IN CZECHOSLOVAKIA

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FOREWORD

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DEVELOPMENTS IN INTERNAL MEDICINE IN CZECHOSLOVAKIA

Following are translations of articles on the above subject, selected from a Czechoslovak source. Source information accompanies each article.

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FIFTEEN YEARS OF INTERNAL MEDICINE IN CZECHOSLOVAKIA

Following is the translation of an article by Dr Karel Bobek in Vnitřní Lekarství (Internal Medicine) Vol VII, No 1, Prague, January 1961, pages 456-468.⁷

The fifteenth anniversary of the liberation of our fatherland by the Soviet army is a welcome opportunity to survey and evaluate the results of the work in all areas of human endeavor. The successes achieved are in their summation a worthy contribution to the nation-wide celebration; the analysis of the failures and the conclusion which can be drawn from them are then a part of the preparation for the next Five-Year Plan.

The Committee of the Czechoslovak Internist Society has delegated me to present on this important occasion a survey of the activity in the field of internal medicine during the past 15 years. The development of the field will be evaluated on one hand from the point of view of specialization and organization, on the other hand from the point of view of the availability of internal medicine service for patients.

After the liberation the number of universities here rose and research in internal medicine took place exclusively in internal medicine clinics until 1951. The victory of the working class built the foundation for the expansion of science and in Paragraph 27 of the law the intensification of research was emphasized as well as the coordination of scientific work, the building of scientific buildings, and the work and training of young scientists. In 1951 was founded at the MZd /Ministerstvo Zdravotnictví -- Ministry of Health Services/ the Center for Health Research together with a scientific council, and the ministry began to build research institutes. The work of these institutes soon developed successfully, but the internal medicine clinics retained an important place in research. To this testifies among other things the fact that in the past year in 20 such clinics work was in progress on nine standard, 113 applied, and 184 faculty research projects. The results of the work of the clinical workers was published in the years 1956-58 in 1296 papers in the local and foreign press. The rich research activity in the clinics is carried out thanks to the qualified university teachers and their enthusiasm, sacrifice, and hard work.

In the past 15 years, many successes have been achieved in research on internal diseases, particularly in solving the causes and pathogenesis of some diseases, as well as in treatment and prevention. In the field of cardiac and vascular diseases, valuable knowledge was gained in the pathogenesis and treatment of hypertensive illness, in the study of ischemic heart disease then were created the methodological prerequisites for following the coronary circulation and its disturbances under the most physio-

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logical conditions. Our research workers also started successfully to administer calcium injections as protection against heart failure in persons with coronary defect operated on with pentothal anesthesia. The relation of electrocardiographic findings and the changes of electrolytes in the particular parts of the heart muscle after closure of the coronary artery was ascertained. The study of the problem of atherosclerosis was begun on a broad basis and significant results were achieved in the following of the metabolism of lipids, further in the study of experimental models in animals, in the study of the relation of atherosclerosis to blood coagulation, and in the study of the epidemiology of atherosclerosis. Deserved attention was in recent years given to research on chronic cor pulmonale; the diseases of the peripheral arteries, veins and lymphatic ducts were also the subject of systematic research. The diagnosis and therapy of venous thrombosis was made more effective and accurate, and directives for its prevention were introduced. A big step forward are the measures against the beginning and the relapses of rheumatic fever by prompt and adequate administration of appropriate forms of penicillin.

Considerable success was also achieved in the field of kidney disorders by the description of the clinical and functional picture of chronic pyelonephritis and by the practical use of an artificial kidney with patients with sudden renal insufficiency.

In the field of gastroenterology the problems of gastric and duodenal ulcers were investigated, further the questions of infectious hepatitis, diseases of the pancreas and of the small and large intestines. A promising method is the depistage of some pathological stomach conditions and the use of determination of uropepsin and an original method of polarographic determination of serum pepsinogen.

In nutritional research, great attention was accorded the study of albumins and fats and to the investigation of the nutrition of some population groups.

In other fields with an internal medicine orientation, for instance in endocrinology, hematology, and rheumatology, research continued with equal success and the results were presented elsewhere. Promising research activity was also developed in the youngest specialty -- gerontology.

The development of internal medicine here did not rely on our own research alone, but also on foreign experience which contributed to it through the means of literature and our scientific workers travelling abroad. The initial difficulties with the importation of foreign literature are today mostly overcome, other foreign contacts (participation at conferences, study trips) will have to be expanded in the future. Otherwise, foreign findings in internal medicine were generally quickly introduced here. I am thinking of laboratory, X-ray and therapeutic methods. Our pharmaceutical industry has an important part in the improvement of the level of therapeutic care in our country. Recently, deserving work has been done by the Commission for Applied Chemotherapy, headed by a Central Commission at the MZd [Health Ministry]. These commissions contribute to the improvement of prescription therapy in a broad way by regularly analysing the prescriptions in districts and regions.

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The use of radioactive isotopes, mainly in the diagnosis of internal diseases, is so far very limited and it will be necessary to expand it. In the future more attention will have to be given to some areas that have been little developed here, like bioclimatology, biometeorology, medical cinematography, cybernetics, aviation physiology, use of the electron microscope, vector cardiography, X-ray amplifiers, etc.

The official representative of internal medicine here is the J.E. Purkyne Czechoslovak Internist Society. It was founded in 1950 and had from the very beginning considerable difficulties because of the existence of several specialized sections with longer tradition, for example the cardiological, endocrinological, gastroenterological section, etc. These sections developed a rich activity, for which they also found support from the workers in research institutes. In the beginning it even seemed that the Internist Society had no reason for existence because of lack of work. In practice this was demonstrated by the fact that the Society did not develop any activities for three years.

In 1955, Professor Vancura assumed the leadership of the Society. He saw in the Society a forum not only for the internists of a general orientation, but also for the representatives of the subdisciplines of internal medicine. The cooperation with other sections, mainly the cardiological, gastroenterological, endocrinological, pneumological sections, showed itself principally in the organization of state-wide meetings, conferences, and workshops. Thus a meeting on hypertension was held during Professor Vancura's lifetime and after his death a series of others, most of which are still living memory, as, for instance, the meeting on "Arteriosclerosis," on "The Significance of Electrolytes for the Clinic," on "Acute Failure of the Liver," on "Extra-articular Signs of Rheumatic Fever," workshops on "Exudative Pleuritis," and on "Bronchitis and Emphysema." Prof Vancura further initiated close cooperation with the Slovak branch of the Internist Society and with several general sections in Plzen, Hradec, Kralove, and Brno. The number of members of the Internist Society has steadily grown, and today 630 members are registered.

In its activity the Internist Society did not limit itself to organizing scientific meetings and conferences, but solved also other, equally important, problems. The Committee of the Society dealt, for instance, with the indications for interruption of pregnancy and for sterilization in cases of internal disease; further, with the question of prekancerose [the last word appears as in the original] etc. The expanded committee proposed the candidates for the Corps of the Chief Internist [Sbor hlavniho internisty.] The Committee of the Society discussed the goal and mission of internal medicine and dealt with the postgraduate training of internists and local physicians.

The Internist Society carries out its function as a unifying organ also through organizing quarterly work-days or half-days instead of the monthly meetings. The special content of these days is furnished by the Internist society together with the component sections, just like the contents of the state-wide conventions, held once a year.

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Of great help in introducing new knowledge into practice is the journal Internal Medicine, founded at the end of 1954 in the place of the discontinued Moravian Medical Papers. Internal Medicine has from the beginning published original material, causal and therapeutic information, group and critical reports, laboratory work, news from meetings, various small items, reports from journals, reviews of books, articles on the history of medicine, personal items, bibliographies, and announcements. The size of the journal is steadily increasing. The number of pages was raised in 1956 from 80 to 96, and in 1959 to 120 pages. The circulation of the journal also increased during the past years and reached this year 2,600 copies. During the five years of its existence the journal has issued 10 special numbers on the anniversaries of our leading internists. Besides local authors Internal Medicine published the work of Soviet workers (Prof Ilyinski, Dr. Kuvalova, Dr. Bakankha) and Polish workers (Dr. Sliwowski). The cooperation of the journal with the Internist Society, of which it is the organ, is very good. The connection between the two organs is on the one hand the Chairman of the Society, who is always the chairman of the editorial board, on the other hand the members of the editorial board, who are mostly members of the Committee of the Society.

The results of the work of our internists are made available to foreign countries through the journal Survey of Czechoslovak Medicine, published in Russian and English, and the journal Cor et Vasa.

A favorite means of raising the general level of the medical science became, besides scientific conferences and meetings and the specialized press, seminar education; clinical-pathological conferences contributed particularly to the improvement of the diagnosis of internal diseases.

Among the significant aspects of the development of medicine, particularly internal medicine, is the organizational side. During the last 20 years, internal medicine, because of its broad scope became more and more specialized, and certain fields, neurology, tuberculosis, and infection, for instance made themselves fully independent. The tendency to become independent grew further and whole areas split off from internal medicine on the basis of organs and of systems. This development occurred in the whole world, and the fast, disproportionate growth of the subspecialties at the expense of internal medicine led to a very unfavorable state of affairs. Warnings against this were soon heard, and they culminated at the International Congress of Internists in Madrid in 1956. There disagreement was expressed with further "atomization" of internal medicine, and the demand was made that the internist be a synthesizing physician, placed above the other specialists with an internal orientation. The Madrid resolution then recommended that the development of disciplines derived from internal medicine be supported only within the framework of general internal medicine as scientific research and conciliar components. This opinion was held previously by some leading workers from among clinicians and administrators, and the position of the Madrid congress only confirmed their concept and speeded up the steps toward correction. In 1957 an eight-member Corps of the Chief Internist was appointed at the Ministry of Health, and when the ministry was reorganized, internal medicine and of its subdisciplines were unified.

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The Corps of the Chief Internist considered it its first task to negotiate with the leading specialists of the subdisciplines the concept, development and organizational integration of their specialties in the framework of general internal medicine. After reaching agreement the conclusions of the negotiations were discussed with the leaders of the councils of the health service sections of KNV [Regional National Committees] and on 29 May 1958 they were approved by the college of the Ministry of Health. In the conception of the whole internal field the present organization of the health services was taken into account and it became clear that the extent of the services to be provided and the division into specialized sectors must vary on various levels: one service must be provided in the region, a different one in the district, another in the local area.

It was approved that in a region the whole internal field would be directed, from a technical point of view, by the regional internist and that the internal medicine department of the KUNZ [Regional Health Center] must assure the highest medical level of care in the region. The KUNZ departments should be equipped accordingly as far as personnel and equipment are concerned. Besides making available the highest quality of internal service, the KUNZ must also assure specialized services in the subdisciplines. The specialists must not work independently and isolated in their department, but must be integrated in the internal medicine department as chief physicians. Under the leadership of the regional internist, they will be able to organize their work according to plan and the needs of the region in such a manner that it will contribute to the improvement of the whole internal service without any tendency to unhealthy isolation.

For the district it first appeared necessary to assure the professional maturity and availability of the internal medicine service and to extend the professional leadership of internists to all local and factory physicians. In each internal medicine department of the OUNZ [District Health Center] there must be provided an appropriate place for the internist in the out-patient service so that he can carry out these duties as well as those connected with the operation of the department itself. This task was given to the health services sections councils of the KNV [abbreviation unidentified] by a decision of 23 January 1958 of the college of the Ministry of Health. Besides stabilizing physicians in the internal medicine department, it was necessary to abolish the minor arrangements for consultation in the subspecialties, and this particularly where these services were not provided by qualified specialists or where they substantially limited the providing of services of the whole internal field.

In the local area, the entire preventive and treatment care is provided for adults by the local area physician, methodically guided by the internist. The local physician treats selected patients, particularly those in need according to the internist's guidelines, and refers patients with difficult diagnoses and therapeutic problems to the internal department of the District Health Center. Only the internal department of the District Health Center refer patients for examination or treatment to the specialized internal department of the KUNZ [Regional Health Center].

The specialists of the subdisciplines are placed in the internal

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medicine department of the KUNZ as specialists (or chief physicians) under the direction of the Chairman of the internal medicine department. From a technical point of view, these specialists are directed by the regional internist, and in cooperation with him they lead and train the other internists in the region. They receive methodological help from the appropriate research institutes after approval from the Corps of the Chief Internists and the Health Ministry. The specialists lead the special conferences within the internal department of the polyclinic of the Regional Health Center, where consultative examinations of patients referred by the internal departments of the District Health Centers or by other departments of the Regional Health Center are made. The specialist has the right to accept -- up to a certain number -- selected patients for examination or care after agreement of the chairman of the internal department of the KUNZ; the specialist's obligation is to cooperate with other specialists of the internal department. The specialist works up the results of the dispensary care in his field and controls the level of the care in the region. The specialists' positions are created by the health services councils of the KNV at the suggestion of the director of the KUNZ and the Regional internist according to the needs of the region. The positions are filled from a list of applicants; an indispensable prerequisite is certification in the particular subdiscipline.

Besides settling the relationship of internal medicine to the subdisciplines, the Corps of the Chief Internist also solved the relationship with some disciplines, the work of which has considerable influence on the development of internal medicine, these are mainly the central laboratory, central X-ray, transfusion service, balneology, physical medicine, rehabilitation etc. The existing dispensary care was also reviewed with the goal in mind of improving quality over quantity.

The Corps also dealt very responsibly with the question of erecting internist dispensaries, with the work of the unified hospital, and approached the solution of the judgement service and its relation to internal medicine. The training of the local physician is also being solved. The cooperation of the Corps with the various parts of the Health Ministry, i.e., the pharmaceutical, technical, supply and marketing sections, developed very well. The Corps acted regularly on proposals for the distribution of imported equipment. The Corps worked in detail on the plan for production of medicaments for the year 1960, and participated in the session of the Central Commission for Applied Chemotherapy. The cooperation of the Corps with the Internist Society is very close, since the chairman of the Czechoslovak Internist Society is a member of the Corps, and the chairman of the Corps is a member of the board of the Internist Society.

In the future, the work of the Corps will be directed by the implementation of the plan which was based on the main goals of the Ministry of Health and the goals of the LP [this abbreviation is not identified] section and is complemented by current questions and needs. The corps has further begun regular meetings with the board of the Internist Society and the regional internists at their state-wide internist conferences; in addition, the Corps meets with the regional internists during their training sessions at the UDL [abbreviation unidentified] in Prague. The results

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of these conferences are positive and will be continued.

If we are to consider the development of internal medicine in its entire breath, we must concern ourselves not only with the service provided in inpatient departments, but also with the outpatient sector. After the liberation, the physicians of the outpatient sector were isolated from other physicians, just as outpatient care was completely divided from hospital care. The chiefs of bed departments rather competed in their offices with outpatient physicians, and the distribution of physicians was very uneven. Physicians were concentrated in towns and wealthier villages; in Prague itself, particularly in its center, there were then a full third of all physicians in the Republic. Hospitals were built, not according to population needs, but according to power and political considerations. Except for insignificant exceptions, factories had no health equipment or industrial physicians. This situation lasted until 1948 when the socialist health system was initiated, expressed in Law 103/51 on preventive treatment care, and Law 4/52 on hygiene and epidemiology.

The most important part which realized these principles in outpatient care is the local area system, introduced state-wide in 1952. The territory of the Republic was divided into small areas in such a way that therapeutic preventive care was most accessible to the whole population. The working arrangements were aimed at eliminating the isolation of the outpatient physicians and at creating a collective manner of working not only among the workers in the outpatient service, but also between outpatient care and hospital care. In evaluating the development so far, one can see that the local area system has proven to be a progressive and correct system, and that in many places excellent results were achieved. The local physician became a social and health influence in his area. These successes, are particularly valuable because the local area system is a new conception and has no tradition yet. In spite of the successes, there exist in the present operation of the area system a number of defects, in organization, as well as in the content of the work. The directives of the health ministry regarding the guidance of the local physician by the internist are not yet fully realized, although the local physician is, through the concentration of his work and the qualifications of the internist, part of the internal medicine department. The cause of the defects rests in the fact that the internists are mostly narrowly oriented toward their work in the hospital and that they are not convinced that the basis of quality care of the population is the local area. A further cause lies in the fact that the decision of the college of the Health Ministry is not fulfilled regarding preference to internal departments in filling positions to enable them to carry out the demands made on them. In districts without hospitals the situation is much worse. The cooperation of the local physician with the public has improved in recent years, particularly good results have been achieved in cooperation with CSCK /abbr. not identified/ with NV and with committees of women. It is better in the country than in the cities.

A further progressive step in the development of outpatient care is the building of polyclinics for area units with 30-50 thousand inhabitants, where specialists are present regularly and where the mutual contact of all physicians for the judging of the health condition of the patient is direct, fast, and complete. The complexity of the resulting impression

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still permits unified medical reporting which will serve the local physician and the specialists at the polyclinic. The medical record is placed in a central filing system, which assumes a considerable part of the administrative work of the physician. The system arranges the appointments of the patients at the medical offices and distributes them evenly and promptly. Thus sudden rushes of patients in the waiting rooms are avoided, the physicians have enough time for examinations, and the work proceeds smoothly. The local physician has at his disposal in the unified health record all findings in chronological order, and he can easily carry out the synthesis of the specialists' findings or, when in doubt, consult with his internist.

Unified inpatient and outpatient care is realized in the unified hospital. It assures on one hand the continuous care of the patient, and on the other hand raises the qualification of the physicians through regular practice in the hospital, which is the professional center of a certain territory. The main prerequisite for the successful operation of the unified hospital is a well organized local and polyclinic system.

The rebuilding of our health care system into a socialist health system causes the largest changes in the outpatient care with local area physicians. Their whole orientation is changed from previous times, when they devoted themselves to treatment for financial reasons only. Today's concentration of prevention aims at having the smallest number of patients in the local area. This cannot be fully achieved if the physician has not changed his former relationship to society, if he is still a prisoner of his former thinking, which aims only at treatment, and if he does not move in closest cooperation with those whose health he is to protect. The local area system forces the physician to participate more and more in public activities and thus create the conditions for good results in his work.

The education of the local physician has to start in medical school, and the present effort to rebuild the curriculum is a good beginning to correct previous conditions. Equally important with the preparation at the university is the postgraduate education which ties in with the university training and complements it. The basic preparation must be in an internal medicine department with practice both in a hospital department and in a local area or a factory. The physician must be admitted to independent practice in the local area only after completing the regular preparation and training with the qualifying attestation in internal medicine of the first degree. The further education of the local physician must, however, continue both professionally and administratively.

The Institute for Advanced Medical Training in Bohemia and in Slovakia has gained great recognition for advanced training of physicians in the field of internal diseases. From 1954 to 1959 the Institute in Prague gave for internists of the first degree, for chiefs of internal departments, for regional internists, including special training in cardiology, altogether 78 courses in which 2257 physicians participated. There were on 1 January 1960 in the CSSR 4,967 internists of the first degree and 739 internists of the 2nd degree. Internists with attestation in the subspecialties have also increased in number, and on 1 January 1960 there were, for instance, 39 internists-cardiologists. The introduction of the qualifying attestation of the 2nd degree for internists meant a great help in raising the level of our internal medicine.

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In order to do his work as well as possible, the internist must have his place of work well equipped. In this regard much has already improved, but much still remains to be corrected and added.

A great problem concerning particularly the field of internal medicine is the overcrowding of inpatient departments, particularly with patients with chronic and incurable diseases. Our health service is conscious of this situation and sees a solution in founding so-called convalescent homes. These may be placed close to hospitals in order to take advantage of the hospital facilities and to maintain through the close connection with the hospital the professional level; economically also this connection might be advantageous. Therefore the establishment of convalescent homes will for the near future have preference over the development of internal departments proper. According to the Third Five-Year Plan an increase in the number of beds in convalescent units of 3,211 beds, i.e. 179.3% is expected in the whole state.

Of the total number of beds, patients of internal medicine departments in 1958 occupied about one fifth (20.8%); the number of physicians allotted to internal hospital departments in the same year was 1,106.11 [sic.]. There were 18.7 beds for each physician position in internal medicine hospital departments. It is expected in the prospective plan that in the outpatient service each territorial area will have 3,750 inhabitants, and according to this count there will be 2.66 physicians for each 10,000 people. In the internal medicine department proper there will be one physician for 10,000 people. The plan provides for inclusion of convalescent units of 2.8 beds per 1,000 persons for internal diseases; the total supply of beds will be 9.96 per 1,000 persons. In regional and university hospitals, the increase is expected to include so-called diagnostic and observation beds, where a correct diagnosis and treatment plan are determined as soon as possible; this will also raise the level of outpatient care. In the Third-Five Year Plan there is an increase of the bed fund for night sanitariums, in the Czech province along 125 more for example. The number of beds in sanitariums in health resorts in our state is expected to rise by 5.2%, especially for patient with circulatory and motor system conditions.

With regard to physicians positions, an increase of 12.7% is expected for the whole state, with particular emphasis given to outpatient care. The number of physicians positions, including dentists, per 10,000 population in outpatient care will rise from 8.9 to 9.7 compared with 1960.

I have attempted to show in which direction the development of our internal medicine has moved during the past 15 years and what results were achieved in that period. At the same time I have pointed out along which road our largest specialty should continue and what the conditions are. The past period was characterized by the search for a unifying concept of internal medicine, and certain organizational and working changes were made in order to assure fully the quality and availability of internal medicine service. The goal of the next years will be to realize broad and effective prevention.

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CZECHOSLOVAK STUDY OF THE ACTION MECHANISM OF
PENETHAMATE HYDROIODIDE (PENESTER)

Following is the translation of an article by V. Sobek
et al in Vnitřní lékařství (Internal Medicine), Vol VII,
No 1, Brno, January 1961, pages 75-80.

Chair of pharmacology and experimental pathology of the department of pediatrics (Chairman: Prof. Dr. H. Raskova). Research Institute for Medicinal Herbs (director: Dr. Z. Cekan).

In an earlier paper it was shown that penethamate hydroiodide (Czechoslovak preparation Penester) accumulates selectively in lung tissue and acts therapeutically, not only by raising the penicillin level and thus by increasing the antimicrobial action, but also with direct broncholytic effect which acts advantageously, especially in bronchial asthma.

The disadvantage of this penicillin preparation is its toxicity and the frequent complications of an allergic nature.

Some of the toxic manifestations, for instance the irritation of the central nervous system, cramps, and collapse, are similar to the toxic effects of procaine. This is understandable if we consider the close chemical relationship between the two substances.

The danger of side-effects is greatest in children, and in certain pathological conditions where the penetration of penethamate into the cerebro-spinal fluid and the brain tissues is increased.

Clinical experience with penethamate has been different in various countries. In certain countries (US) toxic and allergic reactions after penethamate were so frequent that its use was limited, while Czechoslovak clinical experiences have so far been favorable and no more serious complications have been recorded (8).

Our pharmacological analysis has shown that the increased affinity of penethamate for the macroorganism on the one hand increases the danger of side effects, but on the other hand is a very valuable therapeutic contribution.

Therefore we have asked ourselves the question how these side-effects might be eliminated by an appropriate combination of drugs, while preserving or increasing the favorable qualities of penethamate.

Considering the fact that penethamate is used mainly for the

treatment of bronchial asthma and that it can by itself cause reactions of an allergic nature, we thought the combination of antihistamine preparations and penestamate advantageous and submitted it to a pharmacological analysis.

Methods and Materials

We followed the toxicity of Penester (penetamate) and the antihistamine preparations Alfadryl (mephedrylamine), Promethazine and Analergin (antazoline), simultaneously administered, and the combination of Promethazine-Penester, also with a 10 minute premedication of Promethazine (Promethazine was given 10 minutes before the application of Penester).

Penester and the antihistamine preparations were given in certain proportions. Promethazine: Penester with simultaneous administration 1:20, 1:10, 1:5, 1:1, 5:1.

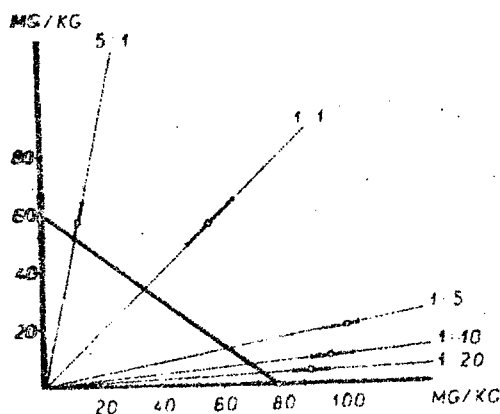
Promethazine: Penester -- Promethazine was given 10 minutes before Penester: 1:20, 1:10, 1:5, 1:1, 5:1, 10:1.

Alfadryl: Penester -- 1:10, 1:5, 1:1, 5:1, 10:1.

Analergin: Penester -- 1:10, 1:5, 1:1, 5:1, 10:1.

The substances were administered into the tail vein of mice. 1000 white mice weighing from 16 to 19 grams were used.

The results were worked up statistically with the isobole method modified according to Roth. On the graphs are marked the LD 50 of Penester and the antihistamine preparations and LD 50 of the listed combinations. The statistical significance is assured, if the limits of the reliability of LD 50 do not reach the additive isobole (diagonal of the axis X and Y).



Graph 1.

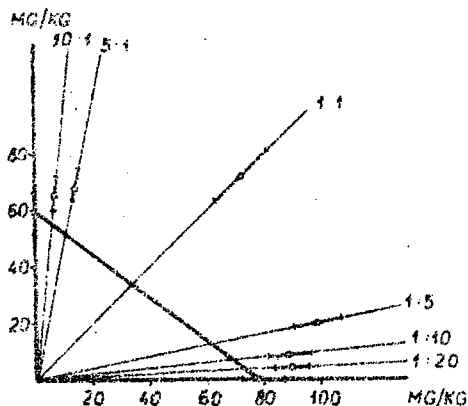
LD 50 of Promethazine and Penester and their combinations.

On axis X, doses of Penester in milligram/kilograms

On axis Y, doses of Promethazine in milligram/kilograms.

We followed in the second part of the experiment on isolated lungs of guinea pigs according to Bhattachary and Delanois (10) the spasmolytic effect of Penester and Analergin, both separately and together in combinations. The investigated substances were introduced into a cannula leading into the pulmonary vein. 25 guinea pigs of both

sexes, weighing 300 to 400 grams were used. Pneumoconstriction and bronchoconstriction were caused by a standard dose of histamine in the amount of 10 μ g in 1 ml of infusion liquid given once.



Graph 2.

LD 50 Promethazine and Penester and their combinations. Promethazine was administered 10 minutes before Penester.

On axis X, doses of Penester

On axis Y, doses of Promethazine

Influence on the effect of the histamine was noted from Penester alone in increasing doses of 1, 2, 4, 8 mg in 1% solution, from Analergin alone in increasing doses of 4, 8, 16, 32 μ g in 0.1% solution, and finally from the simultaneous administration of Penester and Analergin in doses of .5 mg Penester and 4 μ g of Analergin and 1 mg Penester and 8 μ g Analergin.

The Czechoslovak preparations Penester, Analergin, Promethazine Spofa and Alfadryl Spofa were used.

Results

From Graphs number 1, 2, 3 and 4 it is obvious that the antihistamine preparations and Penester act on each other in such a way that the resulting toxicity is lower than the toxicity of the single components of Penester and antihistamine preparation.

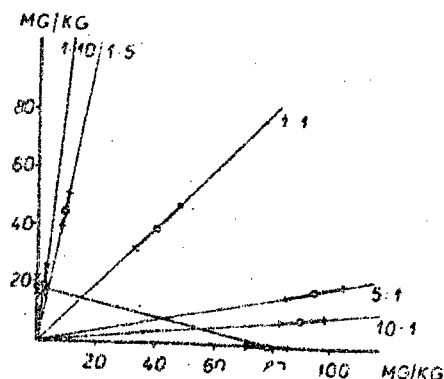
In order to make the relationships clearer, we will list the LD 50 in % with a 95% degree of confidence which express how many % the LD 50 mixture is larger than if the toxicity of the substances had been merely added.

Graph 3.

LD 50 Alfadryl and Penester and their Combinations.

On axis X, doses of Penester

On axis Y, doses of Alfadryl



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1. Promethazine simultaneously with Penester:

| | | |
|------|-------|----------------|
| 1:20 | 121.6 | (103.0-143.5)% |
| 1:10 | 136.6 | (121.6-158.0)% |
| 1:5 | 102.0 | (94.0-111.0)% |
| 1:1 | 170.0 | (139.6-188.6)% |
| 5:1 | 117.5 | (102.2-135.1)% |

2. Promethazine 10 minutes before giving Penester:

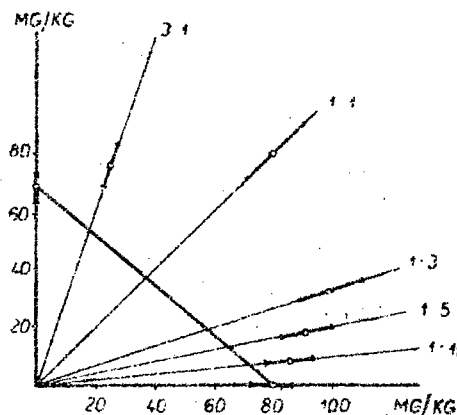
| | | |
|------|-------|----------------|
| 1:20 | 113.5 | (96.2-133.9)% |
| 1:10 | 127.1 | (111.5-148.7)% |
| 1:5 | 157.1 | (139.0-177.5)% |
| 1:1 | 205.7 | (174.3-242.7)% |
| 5:1 | 137.5 | (119.4-156.1)% |
| 10:1 | 121.8 | (104.1-142.5)% |

3. Alfadryl -- Penester:

| | | |
|------|-------|----------------|
| 1:10 | 102.8 | (80.3-131.6)% |
| 1:5 | 216.2 | (180.2-259.4)% |
| 1:1 | 206.7 | (213.4-333.4)% |
| 5:1 | 221.4 | (292.5-358.6)% |
| 10:1 | 158.9 | (138.2-182.7)% |

4. Analergin -- Penester:

| | | |
|------|-------|----------------|
| 1:10 | 121.4 | (107.1-137.2)% |
| 1:1 | 110.0 | (123.9-158.2)% |
| 1:3 | 170.7 | (149.7-194.6)% |
| 1:1 | 216.2 | (189.6-246.5)% |
| 3:1 | 138.9 | (122.9-157.0)% |



Graph 4.

LD 50 of Analergin and Penester and their Combinations.

On axis X, doses of Penester

On axis Y, doses of analergin

We found in experiments on isolated lungs that 10 μ g histamine causes prolonged bronchoconstriction and pneumoconstriction which is not spontaneously relieved. This constriction may be eliminated with Analergin in the dose of 20-40 μ g and with Penester in a dose of 4-8 mg if these substances are given separately, as shown in Graphs 5 and 6.

Simultaneous administering of Penester and Analergin points toward mutual potentiation of the two substances since already .5 mg Penester and 1 μ g Analergin shown a marked effect, even though they do

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not entirely relieve the constriction. A dose of 1 mg Penester and 8 μ g Analergin quickly and completely counteracts the effect of the histamine. The described mixture had a prolonged effect, so that the preparation was after the relief of the histamine spasm insensitive to histamine in the dose of 10 μ g. A typical result is shown in Graph 7.

Discussion

We have shown that antihistamine preparations and Penester (penethamate) interact in such a way that a potentiation of the broncholytic effect and a lowering of their toxicity occur.

Several proportions of these substances were investigated and it was ascertained that the most effective proportion is 1:1 where a lowering of toxicity of over 200% (with regard to Penester and the antihistamine preparation) is achieved with all three antihistamine preparations.

Of course, for clinical use a combination is needed which would increase the tolerance of Penester with the use of a minimal amount of antihistamine.

If we consider our results from this point of view, then the most advantageous combination of Penester and antihistamine is the proportion of 1:3 or 1:5.

From other proportions we do not obtain an increase in the tolerance of Penester, on the contrary, the tolerance of Penester is lowered. Then the toxic effect of the antihistamine preparation begins to appear and the Penester acts as a substance reducing the toxicity of the antihistamines.

As can be seen, for instance, from Graph 4, 38 mg/kg of Analergin lowers LD 50 Penester from 78 mg/kg to 91 mg/kg (proportion 1:5), but 33 mg/kg Analergin increases LD 50 only to 99 mg/kg (proportion 1:3). Higher doses of Analergin do not raise the LD 50 of Penester. 80 mg/kg of Analergin correspond to 80 mg/kg of Penester (proportion 1:1) and 75 mg/kg to only 25 mg/kg Penester.



1 2 2 2

Graph 5



1 2 2 1

Graph 6



1 2 2 1

Graph 7

Graph 5 1=10 μ g of histamine; 2=1 mg of Penester; 2'=2 mg of Penester
2''=4 mg of Penester

Graph 6 1=10 μ g of histamine; 2=10 μ g of analergin; 2'=20 μ g of analergin

Graph 7 1=10 μ g of histamine; 2=0.5 mg of Penester + 4 μ g of analergin;
2'=1 mg of Penester + 8 μ g of analergin

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Similar proportions are found also with the other antihistamine preparations: Promethazine and Alfadryl.

Of the tested antihistamine preparations, Analergin appears to be most advantageous. Even half of the therapeutic doses (60 mg) lowers the toxicity of 300 mg (= about 300,000 units of penicillin) Penester, which is the current therapeutic dose of this antibiotic. Besides, this Alergin is also characterized by low toxicity and good tolerance when injected into the muscle. Therefore we have in the further work concentrated on this antihistamine.

We have shown in isolated lungs that the spasmolytic effect of penethamate is increased in potency through Analergin. A quarter effective dose of both substances suffices to dilate the bronchi.

This finding is a further advantage of the combination of Penester and Analergin, particularly in the treatment of bronchial asthma, where medications with spasmolytic and antibiotic effect are valuable.

Side effects often described after penethamate may be a sign of hypersensitivity to the whole molecule, or to the components penicillin or iodine. Here also the antihistamine preparations can serve advantageously as substances to reduce the risk and raise the effectiveness of the antibiotic therapy.

Antihistamine preparations, especially Analergin, satisfy our requirement, although so far only in animal experiments, of a substance which would increase the therapeutic action of penethamate and would remove the danger of side effects.

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Summary

Antihistamine preparations lower the toxicity of penethamate hydroiodide and increase its broncholytic qualities.

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